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(54) Title: DERIVATIVES OF 2,2,4-TRISUBSTITUTED TETRAHYDROFURAN AS ANTIFUNGAL AGENTS

(57) Abstract: The present invention relates to derivatives of 2,2,4-trisubstituted tetrahydrofuran as potential antifungal agents. This invention also relates to pharmaceutical compositions containing the compounds of the present invention and their use in treating and/or preventing the fungal infections in mammals, preferably humans.

DERIVATIVES OF 2,2,4-TRISUBSTITUTED TETRAHYDROFURAN AS ANTIFUNGAL AGENTS

FIELD OF THE INVENTION

The present invention relates to derivatives of 2,2,4-trisubstituted tetrahydrofuran as potential antifungal agents.

This invention also relates to pharmaceutical compositions containing the compounds of the present invention and their use in treating and/or preventing the fungal infections in mammals, preferably humans.

BACKGROUND OF THE INVENTION

Life-threatening, systemic fungal infections continue to be a significant problem in health care. In particular, patients who become "immunocompromised" as a result of diabetes, cancer, prolonged steroid therapy, organ transplantation anti-rejection therapy, the acquired immune deficiency syndrome (AIDS) or other physiologically or immunologically compromising syndromes, are especially susceptible to opportunistic fungal infections.

Since the 1950's and until recently, the key opportunistic fungal pathogens were *Candida albicans*, *Aspergillus fumigatus* and Zygomycetes, which cause mucormycosis, a rapidly fatal infection especially in diabetic patients. Today, non-albicans *Candida* isolates have become more frequent, as have other *Aspergillus* species. *Candida* species are now the fourth most common cause of nosocomial blood stream infection and they are associated with an extremely high mortality rate of 40%. From 1980 to 1990, the incidence of fungal infections in the US hospitals nearly doubled, from approximately 2 to 3.85 per 1000 patient days. The most marked increase in fungal infection rates occurred not only in transplant units or oncology centres, but also in surgical services. These changing patterns demonstrate that fungal infections are no longer limited to the most severely immunocompromised patients.

During the past two decades, a substantial shift in the epidemiology of candidemia due to different *Candida* species has occurred. In the 1960's and 1970's *Candida albicans* accounted for 85-90% of candidemia. In 1999 however, only 42% of candidemia cases were caused by *C.albicans*, while non-albicans *Candida* accounted for the remainder.

Cryptococosis is a leading cause of morbidity among the AIDS patients. The incidence of life threatening cryptococcal infection among these patients have been estimated to vary from 10 to 30%; 10-20% of the patients die during initial therapy and 30 to 60% patients succumb within a year. *Penicillinium marneffei* has been frequently isolated from HIV positive patients, especially in Southeast Asia.

The most common causative agent of mucormycosis is *Rhizopus*, a common bread mould that lives on any organic material. Other pathogens include *Mucor, Rhizomucor and Absidia.* Zygomycetes include twenty different fungi, all appearing the same histologically. The severely immunocompromised patient may become infected with Zygomycetes via respiratory inhalation.

Fusarium is the most prevalent plant fungus worldwide, and it is now recognized as a human pathogen as well. *Fusarium* infections can occur in immunocompetent or immunosuppressed individuals. *Fusarium* infection is life threatening and associated with a poor prognosis.

Penicillium marneffei is an environmental fungi that can cause serious, life threatening infections in immunosuppressed patients. *Penicillium marneffei* has gained particular attention during the AIDS pandemic, as it may produce disease that is clinically indistinguishable from disseminated histoplasmosis.

Invasive aspergillosis has become a leading cause of death, mainly among patients suffering from acute leukaemia or after allogenic bone marrow transplant and after cytotoxic treatment of these conditions. It also occurs in patients with condition such as AIDS and chronic granulomatous disease. At present, only Amphotericin B and itraconazole are available for treatment of aspergillosis. In

spite of their activity *in vitro*, the effect of these drugs *in vivo* against *Aspergillus fumigatus* remains low and as a consequence mortality from invasive aspergillosis remains high.

Although the first agent with antifungal activity, Griseofulvin was isolated in 1939 and the first azole and polyene antifungal agents were reported in 1944 and 1949, respectively (*Clin. Microbiol. Rev., 1988; 1:187*), it was not until 1960 that Amphotericin B (*I.J. Am. Acad, Dermatol, 1994; 31:S51*), which is still the "gold standard" for the treatment of severe systemic mycoses, was introduced (*Antimicrob. Agents Chemother. 1996; 40:279*)). Despite the general effectiveness of Amphotericin B, it is associated with a number of complications and unique toxicities that limit its use. Furthermore, the drug is poorly absorbed from the gastrointestinal tract necessitating intravenous administration and also penetrates poorly into the cerebrospinal fluid (CSF) of both normal and inflamed meninges. The problems associated with Amphotericin B stimulated search for newer agents.

By 1980, members of the four major classes of antifungal agents, *viz.* polyenes, azoles, morpholines and allylamines had been identified. And advances made during the 1990's led to the addition of some new classes such as the Candins, and the Nikkomycins (*Exp. Opin. Investig. Drugs, 1997; 6:129*). However, with 15 different marketed drugs worldwide, (*Drugs, 1997; 53:539*) the azoles are currently the most widely used and studied class of antifungal agents.

Azole antifungal agents prevent the synthesis of ergosterol, a major component of fungal plasma membranes, by inhibiting the cytochrome P-450 dependent enzyme lanosterol demethylase (referred to as 14-α-sterol demethylase or P-450 $_{DM}$). This enzyme also plays an important role in the cholesterol synthesis in mammals. When azoles are present in therapeutic concentrations, their antifungal efficacy is attributed to their greater affinity for fungal P-450$_{DM}$ than for the mammalian enzyme (*Curr. Opin. Chem. Biol., 1997; 1:176*).

The azole antifungals currently in clinical use contain either two or three nitrogens in the azole ring and are thereby classified as imidazoles (e.g. ketoconazole, miconazole and clotrimazole) or triazoles (e.g. itraconazole and fluconazole),

respectively. With the exception of Ketoconazole, use of the imidazoles is limited to the treatment of superficial mycoses, whereas the triazoles have a broad range of applications in the treatment of both superficial and systemic fungal infections. Another advantage of the triazoles is their greater affinity for fungal rather than mammalian cytochrome P-450 enzymes.

The use of Ketoconazole is severely restricted partly due to its poor toxicity and pharmacokinetic profile and also the fact that none of the opportunistic fungal infections like aspergillosis, candidemia and cryptococcosis are responsive to it (*Antifungal Agents, pgs 401-410 In. G.L: Mandel, J.E. Bennett and R.Dolin (ed.) Principles and practice of infectious diseases, 4th ed. Churchill Livingstone, Inc. New York, N.Y*). Fluconazole is the current drug of choice for treatment of infections caused by *Candida* species and *C. neoformans*. However, management of serious infectious due to *Candida* species, are becoming increasingly problematic because of rising incidence of non-albicans species and the emergence non-albicans isolates resistant to both amphotericin B and the newer azoles. (*Am. J. Med., 1996; 100:617*). Also, fluconazole's spectrum suffers because it has only weak inhibitory activity against isolates of *Aspergillus* species. With regard to the prevention of invasive aspergillosis, a number of antifungal regimens have been suggested for neutropenic patients but only itraconazole has been considered for primary prophylaxis. However, its activity in the clinic remains mixed as it shows variable oral availability, low solubility and very high protein binding besides causing ovarian cancer in animals.

Voriconazole, the fluconazole analog launched recently by Pfizer exhibits 1.6 and 160 fold greater inhibition of ergosterol $P450_{DM}$ in *C. albicans* and *A. fumigatus* lysates, respectively, compared to fluconazole (*Clin. Microbiol. Rev., 1999; 12:40*). The drawbacks associated with voriconazole are its non-linear pharmacokinetic profile besides some concern regarding its ocular toxicity. The development of some of the earlier compounds which included SCH 39304 (Genoconazole), TAK-187, SCH-42427 (Saperconazole), BAY R-8783 (Electrazole) and D-0870 had to be discontinued as a result of safety concerns.

ER-30346 (Ravuconazole), the fluconazole analog under development shows anti-aspergillus profile, at best only equal to that of itraconazole. Schering Plough's compound SCH 56592 (Posaconazole) shows potent broad spectrum activity against primary opportunistic fungal pathogens including *Candida* spp., *C. neoformans* and *Aspergillus* spp. However, it has a pharmacokinetic profile similar to that of itraconazole and is not detectable in CSF, even when the serum drug concentration after several days of treatment are 25 to 100 times above the MIC for the most resistant *C. neoformans.* (*Antimicrobial Agents and Chemother, 1996; 40:1910, 36th interscience Conference on Antimicrobial agents and chemotherapy, September 1996, New Orleans Abst. Drugs of the Future, 1996; 21:20*).

The limited spectrum of antifungal activity, toxicity and lack of both an intravenous and an oral formulation for the same drug limit the likelihood of a successful patient outcome with available therapies.

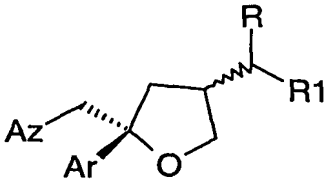
Voriconazole was designed to retain the parenteral and oral formulation advantage of fluconazole while extending its spectrum to moulds, insufficiently treated yeasts and less common fungal pathogens. But though oral bioavailability of voriconazole is high, there is saturable metabolism which results in a more than proportional increase in exposure with increased oral and IV doses. Inter-individual variability in voriconazole pharmacokinetics is high and concerns about its occular toxicity potentials remain to be resolved.

Caspofungin is the first member of a new class of antifungal drugs (echinocandins). It reduces the synthesis of β(1,3)D-glucan, an essential structural cell wall component of fungi . The cell wall is a component of fungal cells that is not found in mammalian cells and loss of cell wall glucan results in osmotic fragility of the fungal organism. The activity of the drug on the cell wall is accomplished indirectly by non competitive inhibition of a gene whose product is a cell membrane protein responsible for glucan synthesis. But caspofungin is not active against *Cryptococcus neoformans* and is available only for IV use.

Thus, the antifungals in the market, as well as under development suffer with drawbacks such as toxicity, narrow spectrum of activity and fungistatic profile rather than fungicidal. Some of them also exhibit drug-drug interactions and as a result, therapy becomes complex. In view of the high incidence of fungal infections in immunocompromised patients and the recent trends for the steady increase of the population of such patients, demands for new antifungal agents with broad spectrum of activity and good pharmacokinetic properties has increased.

SUMMARY OF THE INVENTION

The object of the present invention is to provide compounds of Formula I,



Formula I

and its pharmaceutically acceptable salts, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs, or pharmaceutically acceptable solvates and pharmaceutical compositions containing these compounds which have anti fungal activity and overcome the problems associated with the azole compounds described in the prior art.

Accordingly, the present invention provides derivatives of 2,2,4-trisubstituted tetrahydrofuran compounds of Formula I.

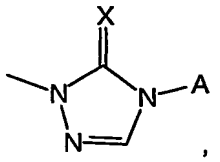
wherein:

Az is a five to seven membered heterocyclic ring having one to four heteroatoms selected from N, S, or O; the preferred heterocyclic ring is 1,2,4-triazol-1-yl;

Ar is a five to seven membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of oxygen nitrogen and sulphur; phenyl or a substituted phenyl group having one to three substituents independently selected from halogen (e.g. chlorine, fluorine, bromine or iodine), nitro, cyano, lower (C_1-C_4) alkyl, lower (C_1-C_4) alkoxy or perhalo lower (C_1-C_4) alkyl, perhalo lower (C_1-C_4) alkoxy; the preferred heterocyclic rings are thienyl and pyridyl;

R is H or methyl;

R_1 is selected from the group consisting of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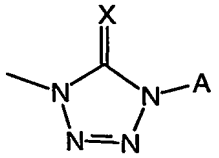
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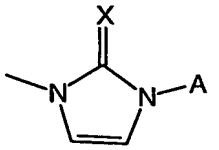
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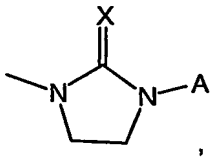
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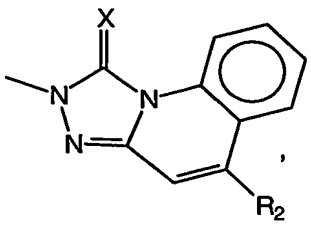
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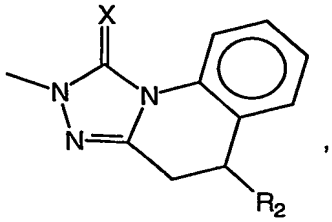

,

wherein

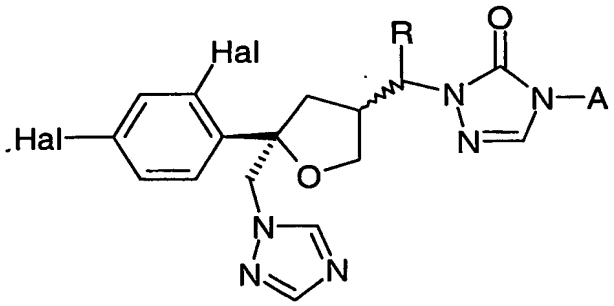
X is selected from the group consisting of CH_2, O, S and SO_2;

R_2 is hydrogen or lower(C_1-C_4) alkyl;

A is hydrogen, lower (C_1-C_4) alkyl, phenyl or phenyl substituted by one or more of groups independently selected from halogen (e.g. chlorine, fluorine, bromine or iodine atom), nitro, cyano, hydroxy, lower(C_1-C_4) alkyl, lower(C_1-C_4) alkoxy, perhalo lower(C_1-C_4)alkoxy or perhalo lower (C_1-C_4) alkyl, substituted or unsubstituted five or six membered heterocyclyl ring system containing one to four hetero atoms chosen from N, O and S, said heterocyclyl substituents being (C_1-C_8) alkanoyl, lower (C_1-C_4) alkyl, lower (C_1-C_4) alkoxy carbonyl, N, N-di(lower alkyl) (C_1-C_4) amino carbonyl, aminothiocarbonyl, N-lower(C_1-C_4) alkyl aminothiocarbonyl, N,N-di(lower alkyl) (C_1-C_4) aminothiocarbonyl, lower (C_1-C_4)

alkyl sulfonyl, phenyl substituted lower (C_1-C_4) alkyl sulfonyl, N-lower(C_1-C_4) alkylamino, N, N-di(lower alkyl) (C_1-C_4) amino, 1,3-imidazol-1-yl, 2-loweralkyl (C_1-C_4) sulfenyl-1,3-imidazol-1-yl, pyridinyl, thiazolyl, 1,2,4 triazol-4-yl or phenyl or phenyl substituted by one or more of groups independently selected from halogen (chlorine, fluorine, bromine or iodine), perhalo lower(C_1-C_4) alkyl, perhalo lower(C_1-C_4) alkoxy, (C_2-C_8) alkanoyl, lower(C_1-C_4) alkyl, lower(C_1-C_4) alkyl substituted by one or more hydroxy group, lower(C_1-C_4) alkoxy, nitro, cyano, hydroxy, 1,2,4-triazolyl, 1,3-imidazolyl, 1,2,3,4-tetrazolyl.

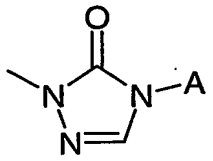
The more preferred compounds of the present invention are the compounds of Formula II



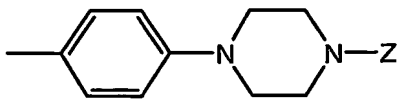
Formula II

(Formula I, wherein: Az is 1,2,4-triazo-1-yl; R is H, CH_3; Ar is 2, 4-dihalo substituted phenyl,

and R_1 is



wherein A is the same as defined earlier and preferred A is



wherein

Z is a hydrogen, (C_1-C_8) alkanoyl, lower alkyl, (C_1-C_8) perhaloalkanoyl, or phenyl, phenyl substituted by one or more of groups independently selected from nitro, cyano, halogen (chlorine, fluorine bromine, iodine) perhalo lower(C_1-C_4) alkyl, perhalo lower(C_1-C_4) alkoxy,(C_2-C_8) alkanoyl, lower(C_1-C_4) alkyl, lower (C_1-C_4) alkyl substituted by one or more hydroxy group, lower(C_1-C_4) alkoxy, 1,3-imidazolyl, 1,2,4-triazolyl, 1,2,3,4-tetrazolyl, or OCH_2Y ; wherein

Y is phenyl or phenyl substituted by one or more of groups independently selected from nitro, cyano, halo, perhalo lower alkyl, (C_2-C_8) alkanoyl lower alkyl, hydroxy, lower alkyl substituted by one or more hydroxy group, lower alkoxy, 1,3-imidazolyl, 1,2,4-triazolyl or 1,2,3,4-tetrazolyl; hal is selected from the group consisting of chlorine, fluorine, bromine and iodine atoms and preferred halo is fluorine atom.

Pharmaceutically acceptable salts are non toxic acid addition salts, formed by adding inorganic or organic acids to the compounds of the present invention, by methods well known in the art.

It is also an object of the invention to provide a method for synthesis of the novel compounds.

The present invention also relates to a method of treating or preventing fungal infections in a mammal by administering to said mammal compositions containing the compounds of the present invention.

The present invention also includes within its scope prodrugs of Formulae I and II. In general, such prodrugs will be functional derivatives of the compound which readily get converted *in vivo* into defined compounds. Conventional procedures for the selection and preparation of suitable prodrugs are known.

Other advantages of the invention will be set forth in the description which follows, and in part will be apparent from the description or may be learned by the practice of the invention.

The illustrated list of compounds of Formula I include

2-[(5R,3R)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl) furan-3-yl-methyl]-4-{4-[4-(phenyl)-1-piperazinyl]-chlorophenyl}-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone (Compound No. 1),

2-[(5R,3S)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(phenyl)-1,2,4-triazol-1-yl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone (Compound No. 2),

2-[(5R,3S)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(hydroxyphenyl)-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone (Compound No. 3),

2-[(5R,3R)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(1,2,4-triazol-1-yl-methyl)-phenyl-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone (Compound No. 4),

2-[(5R,3S)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-{4-[4-(phenyl)-1-piperazinyl]-chlorophenyl}-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone (Compound No. 5),

2-[(5R,3S)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(benzyloxy)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone (Compound No. 6),

2-[(5R,3S)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-{4-[4-[4-(benzyloxy)-phenyl]-1-piperazinyl]-phenyl}-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone (Compound No. 7),

2-[(5R,3R)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone (Compound No. 8),

2-[(5R,3R)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(1,2,3,4-tetrazol-1-yl)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone (Compound No. 9),

2-[(5R,3S)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(2,4-dichlorobenzyloxy)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone (Compound No. 10),

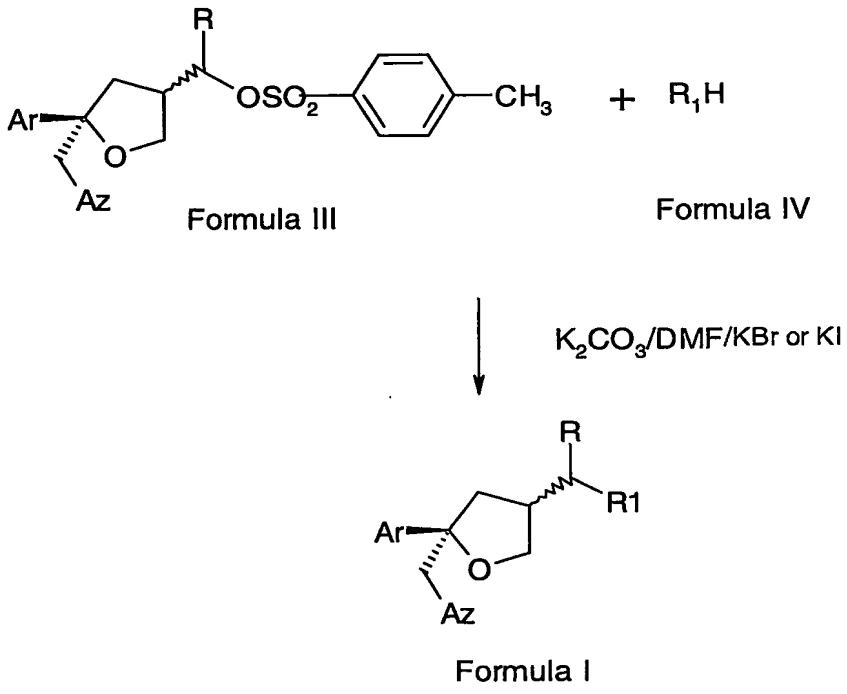
2-[(5R,3R)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-{4-[4-[4-(benzyloxy)-phenyl]-1-piperazinyl]-phenyl}-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone (Compound No. 11),

2-[(5R,3R)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(2,4-dichlorobenzyloxy)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone (Compound No. 12).

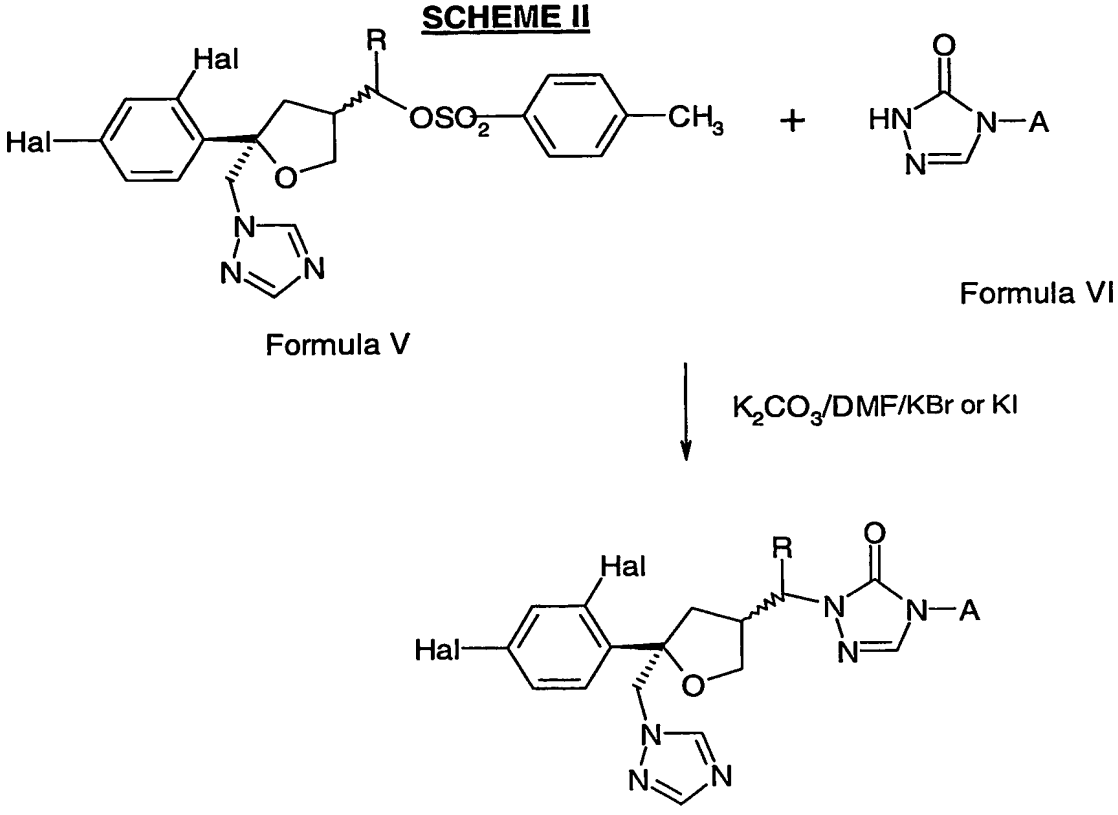
DETAILED DESCRIPTION OF THE INVENTION

In order to achieve the above mentioned objectives and in accordance with the purpose of the invention as embodied and broadly described herein, there is provided a process for the synthesis of compound of Formula I and Formula II, as shown in Schemes I and II.

SCHEME I



SCHEME II



Formula V

Formula VI

K_2CO_3/DMF/KBr or KI

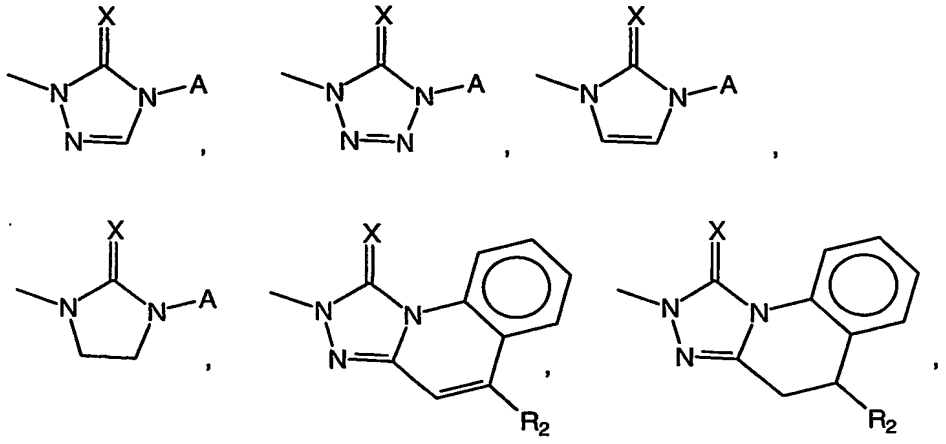
Formula II

In scheme I, there is provided a process for preparing a compound of Formula I, which comprises reacting a compound of Formula III with a compound of Formula IV wherein Az is a five to seven membered heterocyclic ring having one to four heteroatoms selected from N, S, or O; the preferred heterocyclic ring is 1,2,4-triazol-1-yl.

Ar is a five to seven membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of oxygen nitrogen and sulphur; phenyl or a substituted phenyl group having one to three substituents independently selected from halogen (e.g. chlorine, fluorine, bromine or iodine), nitro, cyano, lower (C_1-C_4) alkyl, lower (C_1-C_4) alkoxy or perhalo lower (C_1-C_4) alkyl, perhalo lower (C_1-C_4) alkoxy; the preferred heterocyclic rings are thienyl and pyridyl;

R is H or methyl;

R_1 is selected from the group consisting of



wherein

X is selected from the group consisting of CH_2 , O, S and SO_2;

R_2 is hydrogen or lower (C_1-C_4) alkyl;

A is hydrogen, lower (C_1-C_4) alkyl, phenyl or phenyl substituted by one or more of groups independently selected from halogen (e.g. chlorine, fluorine, bromine or iodine atom), nitro, cyano, hydroxy, lower(C_1-C_4) alkyl, lower(C_1-C_4) alkoxy, perhalo lower(C_1-C_4)alkoxy or perhalo lower (C_1-C_4) alkyl, substituted or unsubstituted five or six membered heterocyclyl ring system containing one to four hetero atoms chosen from N, O and S, said heterocyclyl substituents being (C_1-C_8) alkanoyl, lower (C_1-C_4) alkyl, lower (C_1-C_4) alkoxy carbonyl, N, N-di(lower alkyl) (C_1-C_4) amino carbonyl, aminothiocarbonyl, N-lower(C_1-C_4) alkyl aminothiocarbonyl, N,N-di(lower alkyl) (C_1-C_4) aminothiocarbonyl, lower (C_1-C_4) alkyl sulfonyl, phenyl substituted lower (C_1-C_4) alkyl sulfonyl, N-lower(C_1-C_4) alkylamino, N, N-di(lower alkyl) (C_1-C_4) amino, 1,3-imidazol-1-yl, 2-loweralkyl(C_1-C_4) sulfenyl-1,3-imidazol-1-yl, pyridinyl, thiazolyl, 1,2,4 triazol-4-yl or phenyl or phenyl substituted by one or more of groups independently selected from halogen (chlorine, fluorine, bromine or iodine), perhalo lower(C_1-C_4) alkyl, perhalo lower(C_1-C_4) alkoxy, (C_2-C_8) alkanoyl, lower(C_1-C_4) alkyl, lower(C_1-C_4) alkyl substituted by one or more hydroxy group, lower(C_1-C_4) alkoxy, nitro, cyano, hydroxy, 1,2,4-triazolyl, 1,3-imidazolyl, 1,2,3,4-tetrazolyl.

The starting compound of general Formula III can be prepared by the processes as described in the U.S. Patent Nos. 5,661,151; 5,703, 236; and 5,039,676. The starting compound of general Formula IV can be prepared by the processes as

described in the U.S. Patent Nos. 5,371,101 and 6,034,248; Chem. Ber. 1970; 103:1960 and Chem. Ber. 1975; 108:3799. These starting compounds for Scheme I may be suitably adapted using these references to produce the compounds of Formula I.

The reaction of compound of Formula III with the compound of Formula IV may be carried out in the presence of a suitable base selected from the group consisting of sodium hydride, sodium carbonate, potassium carbonate, cesium carbonate and the like. The reaction may be carried out in the presence of solvents like dimethylformamide, dimethyl sulfoxide, toluene, isopropyl alcohol, tetrahydrofuran, ethylene glycol, dimethyl ether (DME), and the like, or mixtures thereof. The reaction temperature may range from 30° - 120°C, preferably at a temperature in the range of 80° - 85°C.

Scheme II shows the synthesis of compounds of the Formula II in which R, A and Halo groups are as defined above.

The preparation comprises condensing 2,2,4-trisubstituted tetrahydrofuran of the Formula V with 4-substitued triazolone of the Formula VI, wherein A is the same as defined before, in the presence of a base and an organic solvent like dimethylformamide, at a temperature ranging from 30-125°C and preferably at 80-85°C, for a period varying between one to several hours to produce the corresponding 1,4-disubstituted triazolones of the Formula II.

In the above schemes, where specific bases and solvents, etc. are mentioned, it is understood that other bases, and solvents known to those skilled in the art may also be used. Similarly, the reaction temperature and duration of the reactions may be adjusted according to the desired needs.

PHARMACOLOGICAL ACTIVITY

Compound of the Formula I and its salts are useful in the curative or prophylactic treatment of fungal infections in animals, including human.

The *in vitro* evaluation of the antifungal activity of the compound of this invention (as shown in Table I) can be performed by determining the minimum inhibitory concentration (MIC) which is the concentration of the test compound in Rosewell Park Memorial Institute (RPMI) 1640 liquid medium buffered with 3-(Morpholino) propane sulfonic acid (MOPS) to pH 7, at which there is significant inhibition of the particular fungi. In practice the National Committee for Clinical Laboratory Standard (NCCLS) M27A document for Candida and Cryptococcus and M38P for Aspergillus was used to determine the MIC were determined and readings recorded only when the Quality Control results fell into the acceptable range. After MIC results had been recorded, 100 µL from each of the well showing no growth was spread over Sabouraud Dextrose Agar (SDA) to determine the minimum fungicidal concentration (MFC).

The *in vivo* evaluation of the compound can be carried out at a series of dose levels by oral or i.v. injection to mice which are inoculated I.V. with the minimum lethal dose of *Candida albicans, Cryptococcus neoformans* or *Aspergillus fumigatus* by the tail vein. Activity is based on the survival of a treated group of mice after the death of an untreated group of mice. For *Aspergillus* and *Cryptococcus* infections, target organs were cultured after treatment to document the number of mice cured of the infection for further assessment of activity.

For human use, the antifungal compound of the present invention and its salts can be administered above, but will generally by administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice for example, they can be administered orally in the form of tablets containing such exciepients as starch or lactose or in capsules or ovules either alone or in admixture with exciepients or in the form of elixirs, solutions or suspensions containing flavoring or coloring agents. They can

be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

Table – I

Organization	MIC of Compounds (g/ml)							
	Compound No.	4	2	6	3	5	7	9
Candida parapsilosis ATCC 22019 (QC)	<0.00025	8	8	0.25	16	0.03	0.125	16
Candida brusei ATCC 6258 (QC)	0.125	16	8	4	16	0.25	8	64
Paecilomyces variotti ATCC 22319 (QC)	Ng	16	8	16	>16	1	1	32
Cryptococcus neoformans I	0.004	8	8	2	8	<0.03	0.06	32
Cryptococcus neoformans M 106	0.016	8	8	2	8	0.125	0.125	8
Histoplasma capsulatum	0.03	16	16	0.5	16	0.25	16	64
Candida tropicalis ATCC 750	0.002	16	0.5	0.06	16	0.03	0.125	8
Candida krusei 766.1	0.125	16	16	8	16	1	16	64
Candida albicans Y-01-19	Ng	16	16	1	8	0.125	16	64
Candida albicans ATCC 36082	0.03	2	0.125	0.03	16	0.03	<0.03	
Candida glabrata 90030	0.5	16	16	2	16	1	16	64
Aspergillus fumigatus 1008	0.25	16	16	16	>16	2	16	>128
Aspergillus fumigatus Si-I	0.25	16	16	16	>16	1	16	≥128
Candida albicans 1122	-	-	-	-	-	-	-	4
Candida albicans 1162	-	-	-	-	-	-	-	64

The invention is explained in detail in the examples given below which are provided by way of illustration only and therefore should not be constrained to limit the scope of the invention.

EXAMPLE 1

Preparation of 2-[(5R,3R)-5-(2,4-difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-{4-[4-(phenyl)-1-piperazinyl]-chlorophenyl}-2,4-dihydro-3(2*H*,4*H*)-1, 2,4-triazolone.

A mixture of (3R,5R)-5-(2,4-difluorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)-methyl]-tetrahydro-3-furanmethanol, 4-toluenesulfonate (0.25gm, 0.556 mmol) and potassium bromide (0.132 gm, 1.113 mmol) in DMF (15 ml) was heated at 80-85°C for 1hour. Potassium carbonate (0.154g, 1.113 mmol) and 4-{4-[4-(chlorophenyl)-1-piperazinyl]-phenyl}-3(2*H*,4*H*)-1,2,4-triazolone (0.178 gm, 0.50 mmol) were added to the above mixture at room temperature and the resultant

mixture was further heated at 80-85°C for 5 hours. After the reaction was over, the mixture was poured over crushed ice and extracted with ethyl acetate (3x50 ml). The combined organic layers were washed with water (3 x 100 ml), and brine (50 ml) successively, then dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to afford an oily residue. Chromatographed the residue on silica gel, eluting with hexane-ethyl acetate (9:1), to afford the title compound as white solid. Yield: 0.285g, (81%).

^{1}HNMR ($CDCl_3$) : δ 8.11(1H, s, triazole-*H*), 7.77(1H, s, triazole-*H*), 7.58(1H, s, triazolone-*H*), 7.41-7.33(2H, m, Ar-*H*), 7.41-7.33(2H, m, Ar-*H*), 7.33(1H, m, Ar-*H*), 7.25-7.22(2H,m, Ar-*H*), 7.02(2H, d, *J*=8.94Hz, Ar-*H*), 6.82-6.78(2H, m, Ar-*H*), 4.66-4.53(2H, dd, J=14.37 & 14.49 Hz, C*H*$_2$-triazole), 4.13-4.07(1H, m, C*H*$_2$-triazolone), 3.90-3.83(1H, m, C*H*$_2$-triazolone),3.79-3.68(2H,m, C-2*H*), 3.36-3.30(8H, m, piperazine-*H*), 2.64-2.53(2H, m, C-4*H* & C-3*H*) and 2.08-2.00(1H, m, C-4*H*)

IR(KBr) : 3445, 2835, 1699(CO), 1498 and 1230 cm^{-1}

MS(positive ion mode) *m/z* : 633.3 [M^++1]

m.p. : 171-175°C

EXAMPLE 2

Preparation of 2-[(5R,3S)-5-(2,4-difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(phenyl)-1,2,4-triazol-1-yl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone.

By following the procedure of Example 1 and reacting (3S,5R)-5-(2,4-difluorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)-methyl]-tetrahydro-3-furanmethanol, 4-toluene sulfonate and 4-[4-(phenyl)-1,2,4-triazol-1-yl]-3(2*H*,4*H*)-1,2,4-triazolone afforded the title compound.

^{1}HNMR ($CDCl_3$) : δ 8.59(1H, s, triazole-*H*), 8.13(1H, s, triazole-*H*), 8.08(1H, s, triazolone-*H*), 7.85-7.78(3H, m, Ar-*H*), 7.69-7.68(3H, m, Ar-*H*), 7.51-7.43(1H, m, Ar-*H*), 6.89-6.80(2H,m, Ar-*H*), 4.56(1H, d, J=14.25 Hz, C*H*$_2$-triazole), 4.35(1H,d, J=14.25 Hz, C*H*$_2$-triazole), 4.14-4.08(1H, m, C*H*$_2$- triazolone), 3.81-3.60(3H, m,

C*H*$_2$-triazolone & C-2*H*), 2.83-2.75(1H, m, C-3*H*), 2.34-2.24(1H, m, C-4*H*) and 2.13-2.06(1H, m, C-4*H*)

IR(KBr) : 3442, 1695(CO), 1529, 1402 and 1276 cm^{-1}

MS(positive ion mode) *m/z* : 506.1 [M$^+$+1]

m.p. : 186-187°C

EXAMPLE 3

Preparation of 2-[(5R,3S)-5-(2,4-difluorophenyl)-tetrahydro-5-(1-1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(hydroxyphenyl)]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone.

The title compound was prepared by an analogous procedure to that described in Example 1 using (3S,5R)-5-(2,4-difluorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)-methyl]-tetrahydro-3-furanmethanol, 4-toluene sulfonate and 4-[4-(hydroxyphenyl)]-3(2*H*,4*H*)-1,2,4-triazolone .

^{1}HNMR ($CDCl_3$+ MeOD) : δ 8.19(1H, s, triazole-*H*), 7.81(1H, s, triazole-*H*), 7.62(1H, s, triazolone-*H*), 7.45-7.40(2H, m, Ar-*H*), 6.92-6.79(4H, m, Ar-*H*), 4.56(1H, d, J=14.23Hz, C*H*$_2$-triazole), 4.45(1H, d, J=14.23 Hz, C*H*$_2$-triazole), 4.17-4.12(1H, m, C*H*$_2$-triazolone), 3.80-3.61(3H, m, C-2*H* & C*H*$_2$-triazolone), 3.36(1H, brs, -OH), 2.78-2.71(1H, m, C-3*H*), 2.50-2.42(1H, m, C-4*H*) and 2.16-2.10(1H, m, C-4H)

IR(KBr) : 3449(OH), 1684(CO), 1515 and 1274 cm^{-1}

MS(positive ion mode) *m/z* : 454 [M$^+$+1]

m.p. : 199.1-201.4^0 C

EXAMPLE 4

Preparation of 2-[(5R,3R)-5-(2,4-difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(1,2,4-triazol-1-yl-methyl)-phenyl-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone.

The title compound was prepared by an analogous procedure to that described in Example 1 using (3R,5R)-5-(2,4-difluorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)-methyl]-

tetrahydro-3-furanmethanol, 4-toluene sulfonate and 4-[4-(1,2,4-triazol-1-yl-methyl)-phenyl]-3(2*H*,4*H*)-1,2,4-triazolone afforded the title compound.

^{1}HNMR ($CDCl_3$) : δ 8.15(1H, s, triazole-*H*), 8.00(1H, s, triazole-*H*), 7.96(1H, s, triazolone-*H*), 7.80(1H, s, triazole-*H*), 7.78(1H, s, triazole-*H*), 7.68-7.56(3H, m, Ar-*H*), 7.44-7.37(2H, m, Ar-*H*), 6.84-6.78(1H, m, Ar-*H*), 5.39(2H, m, C*H*$_2$-triazolone & C*H*$_2$-triazole), 5.09-4.98(2H, m, C*H*$_2$-triazole), 4.61-4.57(1H, m, C-2*H*), 4.13-4.07(1H, m, C-2*H*), 4.10(1H, d, J=5.00 Hz, C*H*$_2$-triazole), 3.84-3.72(1H, m, C-2*H*) and 2.09-2.04(3H, m, C-2*H* & C-4*H*)

IR(KBr) : 3431, 1706(CO), 1503 and 1273 cm^{-1}

MS(positive ion mode) *m/z* : 520 [M^++1]

m.p. : 60-62.7^{0}C

EXAMPLE 5

Preparation of 2-[(5R,3S)-5-(2,4-difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-{4-[4-(phenyl)-1-piperazinyl]-chlorophenyl}-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone.

The title compound was prepared by an analogous procedure to that described in Example 1 using (3S,5R)-5-(2,4-difluorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)-methyl]-tetrahydro-3-furanmethanol, 4-toluene sulfonate and 4-{4-[4-(phenyl)-1-piperazinyl]-chlorophenyl}-3(2*H*,4*H*)-1,2,4-triazolone afforded the title compound.

^{1}HNMR ($CDCl_3$) : δ 8.10(1H, s, triazole-*H*), 7.85(1H, s, triazole-*H*), 7.54(1H, s, triazolone-*H*), 7.49-7.41(1H, m, Ar-*H*), 7.36(2H, d, J=10.75 Hz, Ar-*H*), 7.26-7.23(2H, m, Ar-*H*), 7.01(2H, d, J=8.8Hz, Ar-*H*), 6.91-6.80(4H, m, Ar-*H*), 4.56(1H, d, J=14.23Hz, C*H*$_2$-triazole), 4.32(1H, d, J=14.23Hz, C*H*$_2$-triazole), 4.14-4.09(1H, m, C*H*$_2$-triazolone), 3.78-3.70(2H,m, C-2*H* & C*H*$_2$-triazolone), 3.65-3.58(1H, m, C-2*H*), 3.35-3.32(8H, brm, piperazine-*H*), 2.81-2.74(1H, m, C-3*H*), 2.37-2.28(1H, m, C-3*H* & C-4*H*) and 2.13-2.06(1H, m, C-4*H*)

IR(KBr) : 2833, 1691(CO), 1520, 1498 and 1232 cm^{-1}

MS(positive ion mode) *m/z* : 633.2 [M^++1]

m.p. : 177-178.2^{o}C

EXAMPLE 6

Preparation of 2-[(5R,3S)-5-(2,4-difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(benzyloxy)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone.

The title compound was prepared by an analogous procedure to that described in Example 1 using (3S,5R)-5-(2,4-difluorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)-methyl]-tetrahydro-3-furanmethanol, 4-toluene sulfonate and 4-[4-(benzyloxy)-phenyl]-3(2*H*,4*H*)-1,2,4-triazolone afforded the title compound.

^{1}HNMR ($CDCl_3$) : δ 8.09(1H, s, triazole-*H*), 7.58(1H, s, triazole-*H*), 7.53(1H, s, triazolone-*H*), 7.46-7.35(8H, m, Ar-*H*), 7.06-7.03(2H, m, Ar-*H*), 6.88-6.80(2H, m, Ar-*H*), 5.09(2H, s, OCH_2), 4.55(1H, d, J=14.27Hz, CH_2-triazole), 4.36(1H, d, J=14.23 Hz, CH_2-triazole), 4.13-4.08(1H, m, CH_2-triazolone), 3.79-3.69(2H, m, C-2*H* & CH_2-triazolone), 3.65-3.60(1H, m, C-2*H*), 2.77-2.75(1H, m, C-3*H*), 2.13-2.09(1H, m, C-4*H*) and 2.07-2.05(1H, m, C-4*H*)

IR(KBr) : 3434, 1691(CO), 1517 and 1255 cm^{-1}

Ms(positive ion mode) *m/z* : 545 [M^++1]

m.p. : 128.2-131.7°C

EXAMPLE 7

Preparation of 2-[(5R,3S)-5-(2,4-difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-{4-[4-[4-(benzyloxy)-phenyl]-1-piperazinyl]-phenyl}-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone.

The title compound was prepared by an analogous procedure to that described in Example 1 using (3S,5R)-5-(2,4-difluorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)-methyl]-tetrahydro-3-furanmethanol, 4-toluene sulfonate and 4-[4-[4-[4-(benzyloxy)-phenyl]-1-piperazinyl]-phenyl]-3(2*H*,4*H*)-1,2,4-triazolone afforded the title compound.

^{1}HNMR ($CDCl_3$) : δ 8.08(1H, s, triazole-*H*), 7.84(1H, s, triazole-*H*), 7.46(1H, s, triazolone-*H*), 7.44-7.32(9H, m, Ar-*H*), 7.03-6.94(4H, m, Ar-*H*), 6.85-6.82(3H, m, Ar-*H*), 5.03(2H, s, OCH_2), 4.57(1H, d, J=14.23Hz, CH_2-triazole), 4.38(1H, d, J=14.26Hz, CH_2-triazole), 4.18-4.08(1H, m, CH_2-triazolone), 3.75-3.62(3H, m, C-

2*H* & CH_2-triazolone), 3.38-3.35(4H, m, piperazine-*H*), 3.25-3.23(4H, m, piperazine-*H*), 2.76-2.60(1H, m, C-3*H*), 2.53-2.31(1H, m, C-4*H*) and 2.12-1.96(1H, m, C-4*H*)

IR(KBr) : 3448, 2930, 1693(CO), 1516 and 1271 cm^{-1}

MS(positive ion mode) *m/z* : 705 [M^++1]

m.p. : 166.4-167.8^{0}C

EXAMPLE 8

Preparation of 2-[(5R,3R)-5-(2,4-difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone.

The title compound was prepared by an analogous procedure to that described in Example 1 using (3R,5R)-5-(2,4-difluorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)-methyl]-tetrahydro-3-furanmethanol, 4-toluene sulfonate and 4-[4-(2,2,3,3-tetrafluoropropoxy)-phenyl]-3(2*H*,4*H*)-1,2,4-triazolone afforded the title compound.

^{1}HNMR ($CDCl_3$) : δ 8.29(1H, s, triazole-*H*), 7.83(1H, s, triazole-*H*), 7.62(1H, s, triazolone-*H*), 7.49(2H, d, J=8.70Hz, Ar-*H*), 7.32-7.29(1H, m, Ar-*H*), 7.03(2H, d, J=8.70Hz, Ar-*H*), 6.86-6.80(2H, m, Ar-*H*), 6.23-5.88(1H, ttt, C*H*F_2), 4.65-4.57(1H, m, CH_2-triazole), 4.42-4.34(1H, m, CH_2-triazole), 4.13-4.08(1H, m, CH_2-triazolone), 3.91-3.74(3H, m, C-2*H* & CH_2-triazolone), 2.65-2.51(2H, m, C-3*H* & C-4*H*) and 2.08-2.01(1H, m, C-4*H*)
IR(KBr) : 3446, 1706(CO), 1517, 1136 and 1108 cm^{-1}

MS(positive ion mode) *m/z* : 568 [M^++1]

m.p. : 64.5 - 66.4°C

EXAMPLE 9

Preparation of 2-[(5R,3R)-5-(2,4-difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(1,2,3,4-tetrazol-1-yl)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone.

The title compound was prepared by an analogous procedure to that described in Example 1 using (3R,5R)-5-(2,4-difluorophenyl)-5-[(1*H*-1,2,4-triazol-

1-yl)-methyl]-tetrahydro-3-furanmethanol, 4-toluene sulfonate and 4-[4-(1,2,3,4-tetrazol-1-yl)-phenyl]-3(2*H*,4*H*)-1,2,4-triazolone afforded the title compound.

^{1}HNMR ($CDCl_3$) : δ 8.14(1H, s, triazole-*H*), 7.80(1H, s, triazole-*H*), 7.61(1H, s, triazolone-*H*), 7.44-7.34(3H, m, Ar-*H*), 7.05(2H, d, J=8.42Hz, Ar-*H*), 6.87-6.78(2H, m, Ar-*H*), 4.66 (1H, d, J=14.48Hz, CH_2-triazole), 4.54(1H, d, J=14.35Hz, CH_2-triazole), 4.12-4.07(1H, m, CH_2-triazolone), 3.82-3.69(3H, m, C-2*H* & CH_2-triazolone), 2.64-2.54(2H, m, C-3*H* & C4*H*) and 2.08-2.01(1H, m, C-4*H*)

IR(KBr) : 3490, 2927, 1707(CO), 1521, 1407, 1270 and 1137 cm^{-1}

MS(positive ion mode) *m/z* : 479 [M^++1]

m.p. : 73.7-75.2^{0}C

EXAMPLE 10

Preparation of 2-[(5R,3S)-5-(2,4-difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(2,4-dichlorobenzyloxy)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone.

The title compound was prepared by an analogous procedure to that described in Example 1 using (3S,5R)-5-(2,4-difluorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)-methyl]-tetrahydro-3-furanmethanol, 4-toluene sulfonate and 4-[4-(2,4-dichlorobenzyloxy)-phenyl]-3(2*H*,4*H*)-1,2,4-triazolone afforded the title compound.

^{1}HNMR ($CDCl_3$) : δ 8.09(1H, s, triazole-*H*), 7.84(1H, s, triazole-*H*), 7.56(1H, s, triazolone-*H*), 7.54-7.38(5H, m, Ar-*H*), 7.30(1H, m, Ar-*H*), 7.05-7.03(2H, m, Ar-*H*), 6.88-6.83(2H, m, Ar-*H*), 5.14(2H, s, OCH_2), 4.55(1H, d, J=14.38Hz, CH_2-triazole), 4.36(1H, d, J=14.23Hz, CH_2-triazole), 4.13-4.08(1H, m, CH_2-triazolone), 3.79-3.57(3H, m, C-2*H* & CH_2-triazolone), 2.80-2.73(1H, m, C-3*H*), 2.33-2.29(1H, m, C-4*H*) and 2.12-2.05(1H, m, C-4*H*)

IR(KBr) : 3448, 2929, 1707(CO), 1515, 1246 and 1137 cm^{-1}

MS(positive ion mode) *m/z* : 613 [M^++1]

m.p. : 100.7 -104.7°C

EXAMPLE 11

Preparation of 2-[(5R,3R)-5-(2,4-difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-{4-[4-[4-(benzyloxy)-phenyl]-1-piperazinyl]-phenyl}-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone.

The title compound was prepared by an analogous procedure to that described in Example 1 using (3R,5R)-5-(2,4-difluorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)-methyl]-tetrahydro-3-furanmethanol, 4-toluene sulfonate and 4-{4-[4-[4-(benzyloxy)-phenyl]-1-piperazinyl]-phenyl}-3-(2*H*,3*H*)-1,2,4-triazolone afforded the title compound.

^{1}HNMR ($CDCl_3$) : δ 8.11(1H, s, triazole-*H*), 8.09(1H, s, triazole-*H*), 7.77(1H, s, triazolone-*H*), 7.45-7.32(8H, m, Ar-*H*), 7.04-6.95(6H, m, Ar-*H*), 6.90-6.79(2H, m, Ar-*H*), 5.04(2H, s, OCH_2), 4.62-4.59(2H, m, CH_2-triazole), 4.11(1H, m, CH_2-triazolone), 3.86-3.73(3H, m, C-2*H* & CH_2-triazolone), 3.38-3.35(4H, brm, piperazine-*H*), 3.25-3.23(4H, brm, piperazine-*H*), 2.35-2.25(2H, m, C-3*H* & C-4*H*) and 2.09-2.04(1H, m, C-4*H*)

IR(KBr) : 3421, 2827, 1695(CO), 1516 and 1249 cm^{-1}

MS(positive ion mode) *m/z* : 705 [M^++1]

m.p. :174.5 - 178.5 ^{0}C

EXAMPLE 12

Preparation of 2-[(5R,3R)-5-(2,4-difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(2,4-dichlorobenzyloxy)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone.

The title compound was prepared by an analogous procedure to that described in Example 1 using (3R,5R)-5-(2,4-difluorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)-methyl]-tetrahydro-3-furanmethanol, 4-toluene sulfonate and 4-[4-(2,4-dichlorobenzyloxy)-phenyl]-3(2*H*,4*H*)-1,2,4-triazolone afforded the title compound.

^{1}HNMR ($CDCl_3$) : δ 8.14(1H, s, triazole-*H*), 7.81(1H, s, triazole-*H*), 7.62(1H, s, triazolone-*H*), 7.52-7.45(4H, m, Ar-*H*), 7.37-7.30(2H, m, Ar-*H*), 7.08(2H, d, J=8.90Hz, Ar-*H*), 6.86-6.82(2H, m, Ar-*H*), 5.18(2H, s, OCH_2), 4.65-4.56(2H, dd, J=14.43Hz each, CH_2-triazole), 4.16-4.11(1H, m, CH_2-triazolone), 3.88-3.82(2H,

m, C-2*H*), 3.78-2.76(1H, m, CH_2-triazolone), 2.92-2.57(2H, m, C-3*H* & C-4*H*) and 2.11-2.04(1H, m, C-4*H*)

IR(KBr) : 3448, 2930, 1706(CO), 1514, 1246 and 1137 cm^{-1}

MS(positive ion mode) *m/z* : 613 [M^++1]

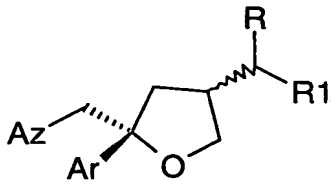
m.p. : 70-71.2°C

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims without further elaboration, it is believed that one skilled in the art can, using the preceding description utilize the present invention to its fullest extent. Therefore, the examples herein are to be construed as merely illustrative and not limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

We Claim:

1. A compound having the structure of Formula I,

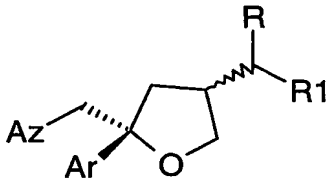


Formula I

and its pharmaceutically acceptable salts, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs , pharmaceutically acceptable solvates,

wherein

Az is a five to seven membered heterocyclic ring having one to four



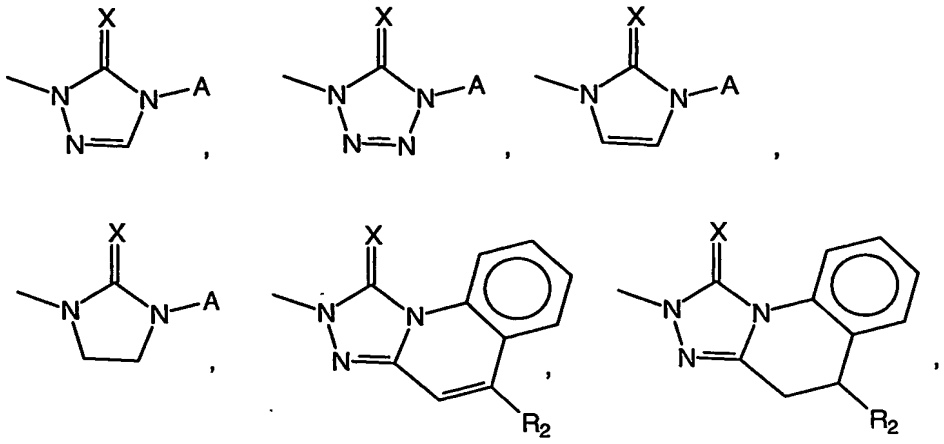
Formula I

heteroatoms selected from N, S, or O; the preferred heterocyclic ring is 1,2,4-triazol-1-yl ;

Ar is a five to seven membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of oxygen nitrogen and sulphur; phenyl or a substituted phenyl group having one to three substituents independently selected from halogen (e.g. chlorine, fluorine, bromine or iodine), nitro, cyano, lower(C_1-C_4) alkyl, lower (C_1-C_4) alkoxy or a perhalo lower (C_1-C_4) alkyl, perhalo lower(C_1-C_4) alkoxy ; the preferred heterocyclic rings are thienyl and pyridyl;

R is H or methyl;

R_1 is selected from the group consisting of



wherein

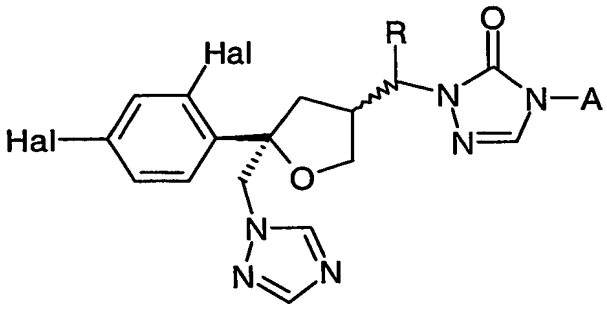
X is selected from the group consisting of CH_2 , O, S and SO_2;

R_2 is hydrogen or lower(C_1-C_4) alkyl;

A is hydrogen, lower(C_1-C_4) alkyl, phenyl or phenyl substituted by one or more of groups independently selected from halogen (e.g. chlorine, fluorine, bromine or iodine atoms), nitro, cyano, hydroxy, lower(C_1-C_4) alkyl, lower (C_1-C_4) alkoxy or perhalo lower (C_1-C_4) alkyl, perhalo lower (C_1-C_4)alkoxy ; substituted or unsubstituted five or six membered heterocyclyl ring systems containing one to four hetero atoms chosen from N, O and S, said heterocyclyl substituents being (C_1-C_8) alkanoyl, lower (C_1-C_4) alkyl, lower (C_1-C_4) alkoxy carbonyl, N, N-di(lower alkyl) (C_1-C_4) amino carbonyl, aminothiocarbonyl, N-lower(C_1-C_4) alkyl aminothiocarbonyl, N,N-di(lower alkyl) (C_1-C_4) aminothiocarbonyl, lower (C_1-C_4) alkyl sulfonyl, phenyl substituted lower (C_1-C_4) alkyl sulfonyl, N-lower (C_1-C_4) alkylamino, N, N-di(lower alkyl) (C_1-C_4) amino, 1,3-imidazol-1-yl, 2-loweralkyl(C_1-C_4) sulfenyl-1,3-imidazol-1-yl, pyridinyl, thaizolyl, 1,2,4 triazol-4-yl or phenyl or phenyl substituted by one or more of groups independently selected from halogen (chlorine, fluorine, bromine or iodine), perhalo lower(C_1-C_4) alkyl, (C_2-C_8) alkanoyl, lower(C_1-C_4) alkyl, lower(C_1-C_4) alkyl substituted by one or more hydroxy group, lower(C_1-C_4)

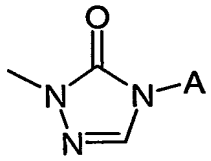
alkoxy, nitro, cyano, hydroxy, 1,2,4-triazolyl, 1,3-imidazolyl, 1,2,3,4-tetrazolyl.

2. The compound of claim 1 having the structure of the Formula II



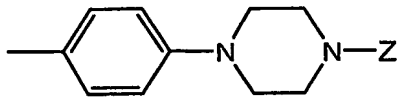
Formula II

(Formula I, wherein Az is 1,2,4-triazol -1-lyl; R is H or CH_3; Ar is 2, 4-dihalo substituted phenyl, Hal is Cl, F, Br or I; and R_1 is



wherein A is the same as defined in claim 1.

3. The compound of claim 2 having the structure of Formula II, wherein A is represented by



Z is a hydrogen, (C_1-C_8) alkanoyl, lower alkyl, (C_1-C_8) perhaloalkanoyl, or phenyl, phenyl substituted by one or more of groups independently selected from nitro, cyano, halogen (chlorine, fluorine bromine, iodine) perhalo lower(C_1-C_4) alkyl, perhalo lower(C_1-C_4) alkoxy; (C_2-C_8) alkanoyl, lower(C_1-C_4) alkyl, lower (C_1-C_4)alkyl substituted by one or more hydroxy

group, lower(C_1-C_4) alkoxy, 1,3-imidazolyl, 1,2,4-triazolyl, 1,2,3,4-tetrazolyl, or OCH_2Y;

wherein Y is phenyl or phenyl substituted by one or more of groups independently selected from nitro, cyano, halo, perhalo lower alkyl, (C_2-C_8) alkanoyl lower alkyl, hydroxy, lower alkyl substituted by one or more hydroxy group, lower alkoxy, 1,3-imidazolyl, 1,2,4-triazolyl or 1,2,3,4-tetrazolyl.

4. A compound selected from the group consisting of:

2-[(5R,3R)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-{4-[4-(phenyl)-1-piperazinyl]-chlorophenyl}-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone,

2-[(5R,3S)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(phenyl)-1,2,4-triazol-1-yl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone,

2-[(5R,3S)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(hydroxyphenyl)-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone,

2-[(5R,3R)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(1,2,4-triazol-1-yl-methyl)-phenyl-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone,

2-[(5R,3S)-5-(2,4,Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-{4-[4-(phenyl)-1-piperazinyl]-chlorophenyl}-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone,

2-[(5R,3S)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(benzyloxy)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone,

2-[(5R,3S)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-{4-[4-[4-(benzyloxy)-phenyl]-1-piperazinyl]-phenyl}-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone,

2-[(5R,3R)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone,

2-[(5R,3R)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(1,2,3,4-tetrazol-1-yl)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone,

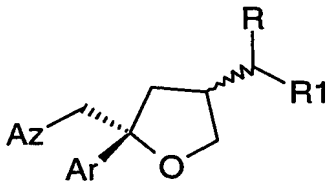
2-[(5R,3S)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(2,4-dichlorobenzyloxy)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone,

2-[(5R,3R)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-{4-[4-[4-(benzyloxy)-phenyl]-1-piperazinyl]- phenyl}-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone,

2-[(5R,3R)-5-(2,4-difluorophenyl)-tetrahydro-5-(1*H*-1,2,4-triazol-1yl-methyl)-furan-3-yl-methyl]-4-[4-(2,4-dichlorobenzyloxy)-phenyl]-2,4-dihydro-3(2*H*,4*H*)-1,2,4-triazolone,

5. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in claim 1 or 4 and a pharmaceutically acceptable carrier or diluent.

6. A method of treating or preventing fungal infection in a mammal comprising administering to said mammal a therapeutically effective amount of a compound having the structure of Formula I



Formula I

and its pharmaceutically acceptable salts, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs , or pharmaceutically acceptable solvates,

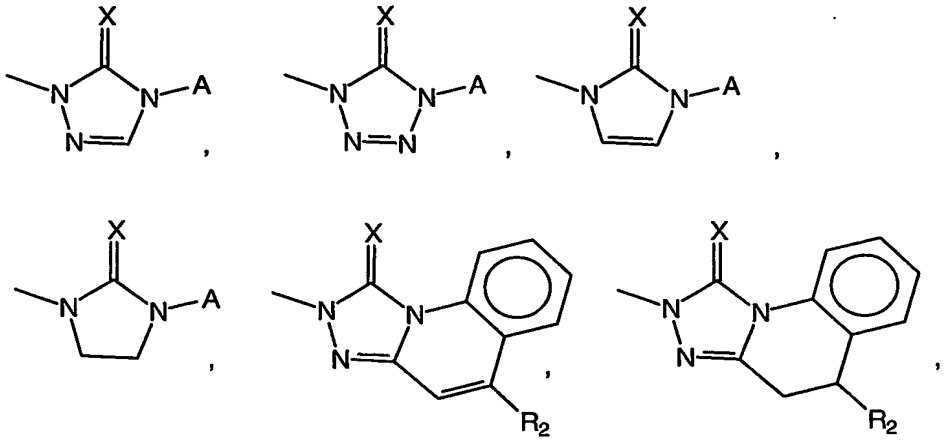
wherein

Az is a five to seven membered heterocyclic ring having one to four heteroatoms selected from N, S, or O; the preferred heterocyclic ring is 1,2,4-triazol-1-yl ;

Ar is a five to seven membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of oxygen nitrogen and sulphur; phenyl or a substituted phenyl group having one to three substituents independently selected from halogen (e.g. chlorine, fluorine, bromine or iodine), nitro, cyano, lower(C_1-C_4) alkyl, lower (C_1-C_4) alkoxy or a perhalo lower (C_1-C_4) alkyl, perhalo lower(C_1-C_4) alkoxy ; the preferred heterocyclic rings are thienyl and pyridyl;

R is H or methyl;

R_1 is selected from the group consisting of



wherein

X is selected from the group consisting of CH_2 , O, S and SO_2;

R_2 is hydrogen or lower(C_1-C_4) alkyl;

A is hydrogen, lower(C_1-C_4) alkyl, phenyl or phenyl substituted by one or more of groups independently selected from halogen (e.g. chlorine, fluorine, bromine or iodine atoms), nitro, cyano, hydroxy, lower(C_1-C_4) alkyl, lower (C_1-C_4) alkoxy or perhalo lower (C_1-C_4) alkyl, perhalo lower (C_1-C_4)alkoxy ; substituted or unsubstituted five or six membered heterocyclyl ring systems containing one to four hetero atoms chosen from N, O and S, said heterocyclyl substituents being (C_1-C_8) alkanoyl, lower (C_1-C_4) alkyl, lower (C_1-C_4) alkoxy carbonyl, N, N-di(lower alkyl)

(C_1-C_4) amino carbonyl, aminothiocarbonyl, N-lower(C_1-C_4) alkyl aminothiocarbonyl, N,N-di(lower alkyl) (C_1-C_4) aminothiocarbonyl, lower (C_1-C_4) alkyl sulfonyl, phenyl substituted lower (C_1-C_4) alkyl sulfonyl, N-lower (C_1-C_4) alkylamino, N, N-di(lower alkyl) (C_1-C_4) amino, 1,3-imidazol-1-yl, 2-loweralkyl(C_1-C_4) sulfenyl-1,3-imidazol-1-yl, pyridinyl, thaizolyl, 1,2,4 triazol-4-yl or phenyl or phenyl substituted by one or more of groups independently selected from halogen (chlorine, fluorine, bromine or iodine), perhalo lower(C_1-C_4) alkyl, (C_2-C_8) alkanoyl, lower(C_1-C_4) alkyl, lower(C_1-C_4) alkyl substituted by one or more hydroxy group, lower(C_1-C_4) alkoxy, nitro, cyano, hydroxy, 1,2,4-triazolyl, 1,3-imidazolyl, 1,2,3,4-tetrazolyl.

7. A method of treating or preventing a fungal infection in a mammal comprising the step of administering to said mammal a therapeutically effective amount of the pharmaceutical composition according to claim 5.

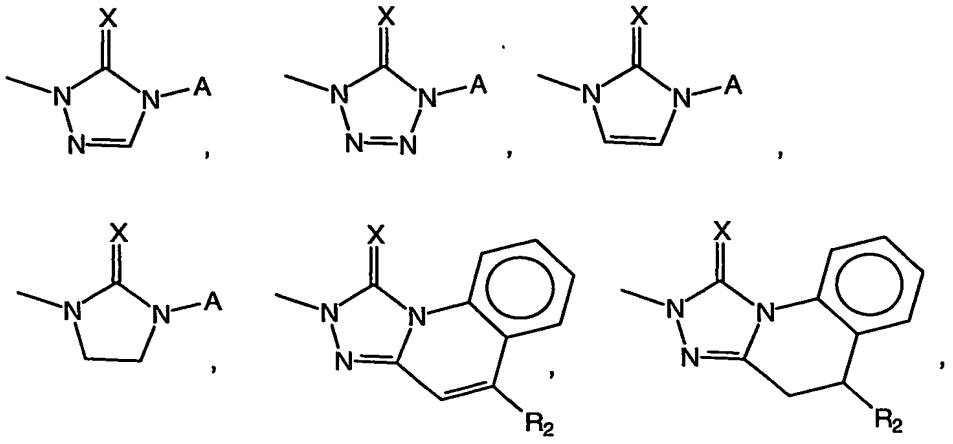
8. A process for preparing a compound of the Formula I, its pharmaceutically acceptable salts, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs, or pharmaceutically acceptable solvates

wherein

Az is a five to seven membered heterocyclic ring having one to four heteroatoms selected from N, S, or O; the preferred heterocyclic ring is 1,2,4-triazol-1-yl ;

Ar is a five to seven membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of oxygen nitrogen and sulphur; phenyl or a substituted phenyl group having one to three substituents independently selected from halogen (e.g. chlorine, fluorine, bromine or iodine), nitro, cyano, lower(C_1-C_4) alkyl, lower (C_1-C_4) alkoxy or a perhalo lower (C_1-C_4) alkyl, perhalo lower(C_1-C_4) alkoxy ; the preferred heterocyclic rings are thienyl and pyridyl;

R is H or methyl;
R_1 is selected from the group consisting of



wherein

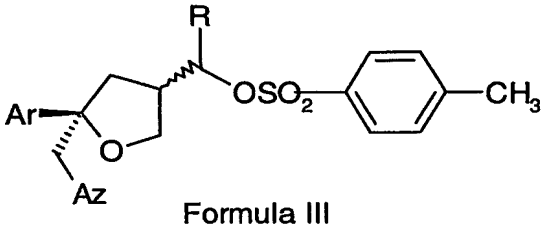
X is selected from the group consisting of CH_2 , O, S and SO_2;

R_2 is hydrogen or lower(C_1-C_4) alkyl;

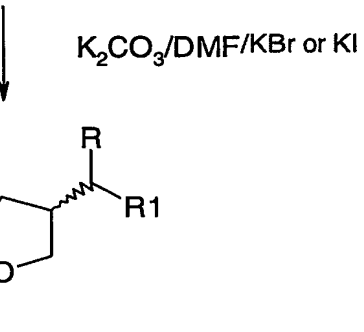
A is hydrogen, lower(C_1-C_4) alkyl, phenyl or phenyl substituted by one or more of groups independently selected from halogen (e.g. chlorine, fluorine, bromine or iodine atoms), nitro, cyano, hydroxy, lower(C_1-C_4) alkyl, lower(C_1-C_4) alkoxy or perhalo lower (C_1-C_4) alkyl, perhalo lower(C_1-C_4)alkoxy ; substituted or unsubstituted five or six membered heterocyclyl ring systems containing one to four hetero atoms chosen from N, O and S, said heterocyclyl substituents being (C_1-C_8) alkanoyl, lower (C_1-C_4) alkyl, lower (C_1-C_4) alkoxy carbonyl, N, N-di(lower alkyl) (C_1-C_4) amino carbonyl, aminothiocarbonyl, N-lower(C_1-C_4) alkyl aminothiocarbonyl, N,N-di(lower alkyl) (C_1-C_4) aminothiocarbonyl, lower (C_1-C_4) alkyl sulfonyl, phenyl substituted lower (C_1-C_4) alkyl sulfonyl, N-lower(C_1-C_4) alkylamino, N, N-di(lower alkyl) (C_1-C_4) amino, 1,3-imidazol-1-yl, 2-loweralkyl(C_1-C_4) sulfenyl-1,3-imidazol-1-yl, pyridinyl, thaizolyl, 1,2,4 triazol-4-yl or phenyl or phenyl substituted by one or more of groups independently selected from halogen (chlorine, fluorine, bromine or iodine), perhalo lower(C_1-C_4) alkyl, (C_2-C_8) alkanoyl, lower(C_1-C_4) alkyl, lower(C_1-C_4) alkyl substituted by one

or more hydroxy group, lower(C_1-C_4) alkoxy, nitro, cyano, hydroxy, 1,2,4-triazolyl, 1,3-imidazolyl, 1,2,3,4-tetrazolyl;

which comprises reacting a compounds of Formula III with a compound of Formula IV as shown below, where all symbols are as defined above.

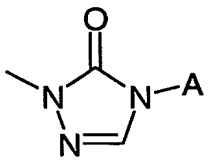


Formula III Formula IV

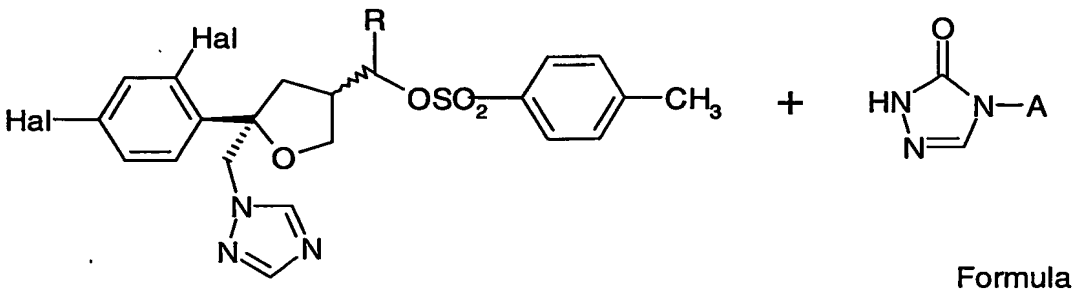


Formula I

9. A process according to claim 8 for preparing a compound of the Formula II (Formula I, wherein Az is 1,2,4-triazol -1-lyl; R is H or CH_3; Ar is 2, 4-dihalo substituted phenyl, Hal is Cl, F, Br or 1; and R_1 is



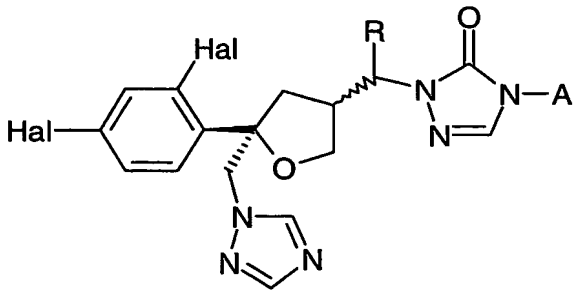
wherein A is the same as defined in claim 1, which comprises condensing 2,2,4 – trisubstituted tetrahydrofuran of the Formula V with 4 – substituted triazolone of Formula VI as shown below:



Formula V

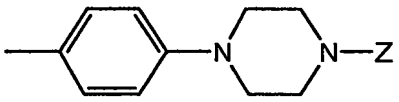
Formula VI

K_2CO_3/DMF/KBr or KI



Formula II

10. A process according to claim 9 for preparing a compound of Formula II, wherein A is represented by



Z is a hydrogen, (C_1-C_8) alkanoyl, lower alkyl, (C_1-C_8) perhaloalkanoyl, or phenyl, phenyl substituted by one or more of groups independently selected from nitro, cyano, halogen (chlorine, fluorine bromine, iodine) perhalo lower(C_1-C_4) alkyl, perhalo lower(C_1-C_4) alkoxy; (C_2-C_8) alkanoyl, lower(C_1-C_4) alkyl, lower (C_1-C_4)alkyl substituted by one or more hydroxy group, lower(C_1-C_4) alkoxy, 1,3-imidazolyl, 1,2,4-triazolyl, 1,2,3,4-tetrazolyl, or OCH_2Y ;wherein

Y is phenyl or phenyl substituted by one or more of groups independently selected from nitro, cyano, halo, perhalo lower alkyl, (C_2-C_8) alkanoyl lower

alkyl, hydroxy, lower alkyl substituted by one or more hydroxy group, lower alkoxy, 1,3-imidazolyl, 1,2,4-triazolyl or 1,2,3,4-tetrazolyl.

11. The process of claim 8 wherein the reaction of compound of formula III and formula IV is carried out in a suitable organic solvent wherein the solvent is selected from the group consisting of dimethylformamide, dimethyl sulfoxide, toluene, isopropyl alcohol, tetrahydrofuran, ethylene glycol, dimethyl ether, and mixtures thereof.

12. The process of claim 8 wherein the reaction of compound of formula III and formula IV is carried out in the presence a suitable base.

13. The process of claim 12 wherein the base is selected from the group consisting of sodium hydride, potassium carbonate, cesium carbonate, and sodium carbonate.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 02/01197

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D521/00 A61K31/4196 A31P31/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A31K A31P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 539 938 A (SCHERING CORP) 5 May 1993 (1993-05-05) Abstract; claim 1. --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 August 2002	05/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Weisbrod, T

3

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KITAZAKI T ET AL: "OPTICALLY ACTIVE ANTIFUNGAL AZOLES. VI.1) SYNTHESIS AND ANTIFUNGAL ACTIVITY OF N-U(1R,2R)-2-(2,4-DIFLUOROPHENYL)-2-HYDROXY-1-METHYL-3-(1H-1,2,4-TRIAZOL-1-YL)PROPYL-N'-(4-SUBSTITUTED PHENYL)-3(2H,4H)- 1,2,4-TRIAZOLONES AND 5(1H,4H)-TETRAZOLONES" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 44, no. 2, 1996, pages 314-327, XP002067032 ISSN: 0009-2363 Page 314, formulae I, II, 1-3. ---	1-13
X	SAAG M S ET AL: "AZOLE ANTIFUNGAL AGENTS: EMPHASIS ON NEW TRIAZOLES" ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, DC, US, vol. 32, no. 1, 1988, pages 1-8, XP000605684 ISSN: 0066-4804	1,6
Y	Page 2: paragraph "Structur". -----	2-5,7-13

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,5,6,8 (all part)

Claim 1, 5-6 and 8 relate to compounds (I) as well as to prodrugs and metabolites thereof. Thus, these claims encompass compounds i.e. prodrugs and metabolites having structures and formulae different from those compounds represented by formula (I). Neither from the description nor from the claims it is apparent which structural features found in formula (I) must necessarily be present in said prodrugs and metabolites, and which structural features may be varied. Therefore, the scope of the claims 1, 5, 6, and 8 is so unclear (Article 6 PCT), that these claims have not been searched insofar as the terms prodrugs and metabolites are concerned.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 02/01197

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6 and 7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1,5,6,8 (all part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 02/01197

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0539938 A	05-05-1993	AT 198888 T	15-02-2001
		AU 665218 B2	21-12-1995
		AU 2916992 A	07-06-1993
		CA 2122270 A1	13-05-1993
		CN 1073944 A ,B	07-07-1993
		CZ 9401027 A3	15-03-1995
		DE 69231661 D1	01-03-2001
		DE 69231661 T2	02-08-2001
		EP 0539938 A1	05-05-1993
		EP 0610377 A1	17-08-1994
		ES 2153364 T3	01-03-2001
		FI 941986 A	29-04-1994
		HR 921145 A1	11-08-1994
		HU 70742 A2	30-10-1995
		JP 7500605 T	19-01-1995
		JP 3210017 B2	17-09-2001
		MX 9206222 A1	01-04-1993
		NO 941589 A	23-06-1994
		NZ 244910 A	26-01-1996
		PL 170743 B1	31-01-1997
		SG 42920 A1	17-10-1997
		SI 9200285 A	30-06-1993
		SK 48894 A3	08-02-1995
		WO 9309114 A1	13-05-1993
		ZA 9208342 A	29-04-1993